plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different perturbation.

REMARKS

The specification has been amended to correct typographical errors discovered by Attorneys for Applicants during review of the application. Claims 1-88 were pending in the application. Claims 51-57, 65-71, and 79-88 have been withdrawn from consideration by the Examiner as directed to non-elected subject matter. Applicants hereby cancel claims 51-57, 65-71, and 79-88 without prejudice to Applicants' right to pursue the subject matter of these canceled claims in related patent applications. Claims 1, 5, 6, 10-11, 18, 23-27, 29-31, 38-39, 44, 50, 58-59, 62-64, and 72-76 have been amended and new claims 89-100 have been added to more particularly point out and distinctly claim the present invention. None of the above-made claim amendments has been made in response to the Examiner's rejection of the pending claims under 35 U.S.C. § 103. Upon entry of the above-made amendments, claims 1-50, 58-64, 72-78, and 89-100 will be pending.

Claim 1 has been amended to include the recitation that each response profile in the plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different perturbation. Support for the amendment is found in the specification at, *e.g.*, page 14, line 31 to page 15, line 8 and page 20, lines 23-24. Claim 1 has also been amended to more particularly point out that common response motifs are identified among sets of cellular constituents that are co-regulated or co-vary under a plurality of perturbations. Support for the amendment is found in the specification at, *e.g.*, page 4, lines 17-21; page 23, lines 23-24; page 33, lines 19-20; and in Fig. 1. Claim 1 has further been amended to more particularly point out that the method is for determining a consensus profile for a *perturbation to a cell type or organism* (emphasis added). Support for the amendment is found in the specification at, *e.g.*, page 3, lines 13-26. Claim 6 has also been amended to accordingly.

Claim 5 has been amended to correct a typographical error.

Claims 10, 11, 24, 27, 30, and 31 have been amended to more particularly point out the invention by deleting "co-varying." Support for the amendments is found in the specification at, *e.g.*, page 23, lines 23-24 and page 33, lines 19-20. Claim 10 and 11 have

also been amended to more particularly point out that the sets of cellular constituents consist of cellular constituents.

Claim 18 has been amended to particularly point out that the Monte Carlo randomization is of *the perturbation index* for the response of each *cellular constituent* across all perturbations (emphasis added). Support for the amendment is found in the specification at page 28, line 29 to page 29, line 13. Claim 18 has also been amended to correct typographical errors.

Claims 23 and 25 have been amended to recite subject matter that appropriately depends on the base claim. Support for the amendment is found in the specification at page 37, lines 19-22 and page 27, line 24 to page 28, line 9.

Claims 26 and 50 have been amended to particularly point out that the Monte Carlo randomization is of *the cellular constituent index* for each response profile *across the measured cellular constituents* (emphasis added). Support for the amendments is found in the specification at page 37, lines 19-23 and page 28, line 29 to page 29, line 13. Claims 26 and 50 have also been amended to correct typographical errors.

Claim 29 has been amended into independent form. Claim 29 has also been amended to more particularly point out that projected response profiles projected onto basis cellular constituent sets, which are defined by co-variation of measurements of cellular constituents under a plurality of perturbations, are used for identifying common response motifs. Support for the amendment is found in the specification at, *e.g.*, page 5, lines 10-13, lines 21-24, and lines 27-29.

Claim 31 has been amended to depend on claim 29 reciting a method wherein the consensus profile is the intersection of the sets of cellular constituents activated or de-activated in the common response motifs. Support for the amendment is found in the specification at page 41, lines 21-24.

Claim 38 has be amended to include the recitation that each response profile in the plurality of response profiles (i) comprising expression measurements of a plurality of genes, and (ii) resulting from a different perturbation. Support for the amendment is found in the specification at, *e.g.*, page 10, line 27 to page 11, line 2; page 14, line 31 to page 15, line 8; and page 20, lines 23-24. Claim 38 has also been amended to more particularly point out that common response motifs are identified among sets of genes that are co-regulated or co-vary

under a plurality of perturbations. Support for the amendment is found in the specification at, *e.g.*, page 23, lines 23-24 and page 33, lines 19-20. Claim 38 has further been amended to more particularly point out that the method is for determining a consensus profile for a *perturbation to a cell type or organism* (emphasis added). Support for the amendment is found in the specification at, *e.g.*, page 3, lines 13-26.

Claim 39 has been amended to more particularly point out that the consensus profile comprising common response motifs among basis cellular constituent sets in a plurality of projected response profiles, each projected response profile in said plurality of projected response profiles (i) resulting from a different perturbation to said type of cell or organism, and (ii) comprising measurements of a plurality of cellular constituents in said type of cell or organism that have been projected onto basis cellular constituent sets, said basis cellular constituent sets being defined by co-variation of measurements of cellular constituents under a plurality of different perturbations, wherein said common response motifs constitute the consensus profile for said perturbations. Support for the amendment is found in the specification at, *e.g.*, page 5, lines 21-24 and lines 27-29, page 14, line 31 to page 15, line 8 and page 20, lines 23-24. Claim 39 has also been amended to more particularly point out that the biological response profile is converting into a projected response profile by projecting measurements of cellular constituents in said biological response profile onto the basis cellular constituent sets.

Claim 44 has been amended to recite that the method comprising grouping of sets of response profiles among a plurality of response profiles, said sets of response profiles consisting of response profiles having similar responses of a first plurality of cellular constituents, each response profile in said plurality of response profiles (i) comprising measurements of a second plurality of cellular constituents, and (ii) resulting from a different perturbation. Support for the amendment is found in the specification at, *e.g.*, page 14, line 31 to page 15, line 8 and page 20, lines 23-24.

Claim 58 has been amended to particularly point out that the claim method comprises identifying *one of more groups of cellular constituents* (emphasis added) in one or more measured response profiles associated with exposure to the drug or drug candidate, which are indicative of a therapeutic effect. Support for the amendment is found in the specification at, *e.g.*, page 3, lines 13-26. Claim 58 has also been amended to include the recitation that each

response profile in the plurality of response profiles comprising measurements of a plurality of cellular constituents. Support for the amendment is found in the specification at, *e.g.*, page 14, line 31 to page 15, line 8 and page 20, lines 23-24. Claim 58 has also been amended to more particularly point out that common response motifs are identified among sets of cellular constituents that are co-regulated or co-vary under a plurality of perturbations. Support for the amendment is found in the specification at, *e.g.*, page 4, lines 17-21; page 23, lines 23-24; page 33, lines 19-20; and in Fig. 1.

Claims 59 and 62-64, which depend on claim 58, have also been amended to accordingly. Claim 64 has also been amended to particularly point out that the Monte Carlo randomization is of *the perturbation index* for each cellular constituents *across all* perturbations (emphasis added). Support for the amendment is found in the specification at page 28, line 29 to page 29, line 13.

Claim 72 has been amended to include the recitation that each response profile in the plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different perturbation. Support for the amendment is found in the specification at, *e.g.*, page 14, line 31 to page 15, line 8 and page 20, lines 23-24. Claim 72 has also been amended to more particularly point out that the claim method is for analyzing response data from a biological sample. Claims 73 and 74, which depend on claim 72, have also been amended so that the recitations in these claims agree with the recitations in the base claim.

Claim 75 has been amended to more particularly point out that the biological effect is *an effect on* a biological pathway (emphasis added).

Claim 76 has been amended to more particularly point out that the recited biological effect is the biological effect recited in the base claim.

New claims 89-100 have been added to more particularly point out the invention. In particular, claim 89 recites a method for determining a consensus profile by identifying common response motifs among sets of co-varying cellular constituents. Support for the claim is found in the specification at, *e.g.*, page 5, lines 9-13. New claims 90-96 recite methods for determining a consensus profile by identifying common response motifs among sets of co-varying cellular constituents by cluster analysis. Support for the claims is found in the specification at page 23, line 23 to page 33, line 16. New claim 97 recites methods in

which sets of co-varying cellular constituents comprise cellular constituents which co-vary in the plurality of response profiles. Support for the claim is found in the specification, *e.g.*, at page 38, lines 2-3. New claims 98 and 99 recite methods for analyzing response data from a biological sample by applying the steps (a) and (b) of the base claim in different orders. Support for the claims is found in the specification at page 16, lines 16-21. New claim 100 recites a method of identifying perturbations that similarly affect cellular constituents by grouping a plurality of response profiles that similarly affect cellular constituents. Support for the claim is found in the specification at page 37, lines 17-23, and page 38, lines 7-24.

No new matter has been added by the amendments and the new claims. Entry of the foregoing amendments and the following remarks is respectfully requested.

APPLICANTS' INTERVIEW SUMMARY

Applicants thank Primary Examiner Ardin Marschel and Supervisory Patent Examiner Michael Woodward for the courtesies extended during the interview on June 13, 2000 (hereinafter "the Interview") with Applicant Roland Stoughton and Applicants' representatives Adriane M. Antler and Weining Wang. During the interview, the instant application was first discussed. The claim rejections under 35 U.S.C. § 103(a) were then discussed. The reference cited in the Office Action (U.S. Patent No. 5,800,992) was also discussed as it pertains to the claim rejection under 35 U.S.C. § 103(a).

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During the Interview, Dr. Stoughton first explained the invention as described and enabled in the instant application and recited in the pending claims.

Dr. Antler then explained proposed amendments to claim 1. In particular, Dr. Antler proposed to include the recitation in the amended claim, to more particularly point out the invention, that each response profile in the plurality of response profiles (i) comprises measurements of a plurality of cellular constituents, and (ii) results from a different perturbation.

The interview participants then discussed the claim rejection under 35 U.S.C. § 103(a) over U.S. Patent No. 5,800,992 issued to Fodor et al ("Fodor"). Dr. Stoughton and Dr. Antler explained, for reasons discussed below, that Fodor does not make the claimed invention obvious. In particular, Fodor teaches the use of DNA arrays for sequencing, sequence fingerprinting, and cell typing using markers, and synthesis of the arrays by photolithography.

Fodor contains no hint or suggestion of identifying consensus profiles that are similar motifs in response profiles for different perturbations. The Examiner agreed to reconsider the § 103 rejection.

THE PRESENT INVENTION

The claimed invention relates, *inter alia*, to methods for determining a consensus profile for perturbations and to methods for comparing a biological response profile to a consensus profile. Also claimed are methods for grouping measured response profiles in sets which are associated with similar biological effects, to methods for determining the therapeutic efficacy of a drug or drug candidate, to methods for analyzing response data by grouping cellular constituents and response profiles, to methods for identifying perturbations that affect cellular constituents, and to methods for iterative refinement of cellular constituent sets and clusters of response profiles. In particular, the present invention relates to methods of determining a consensus profile for perturbations, such as perturbations by drugs, by identifying common response motifs among sets of co-varying or co-regulated cellular constituents in a plurality of response profiles resulting from the perturbations. The methods of the invention analyze response profiles, which comprise measurements of a plurality of cellular constituents in a cell in response to a particular set or sets of perturbations, such as drug exposure, targeted mutations, or targeted changes in protein activity or expression, etc. In one claimed embodiment, common response motifs are identified in response profiles that are projected profiles, in which the measurements of cellular constituents are projected onto basis cellular constituent sets. In another example of a claimed embodiment, response profiles are each grouped according to their similarities. In particular, the cellular constituents are grouped or re-ordered into sets of cellular constituents, including co-varying sets of cellular constituents that are, for example, identified by means of a pattern recognition procedure or algorithm, such as a clustering procedure or algorithm, and then common response motifs are identified among the re-ordered sets of co-varying cellular constituents.

THE REJECTIONS UNDER 35 U.S.C. § 103(a)
SHOULD BE WITHDRAWN

Claims 1-50, 58-64, and 72-78 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,800,992 issued to Fodor et al ("Fodor"). The Examiner contends that arrays are used in Fodor to perform hybridization assays over numerous hybridization probe sequences and that the usage of these arrays for drug evaluation and for determining the expression of a multitude of mRNA types are motivated and suggested, thereby anticipating the present invention. Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Fodor discloses the use of arrays for sequencing, sequence fingerprinting, and mapping biological macromolecules (Abstract of Fodor). Fodor also describes cell typing using markers, and synthesis of the arrays by photolithography. In addition, Fodor discloses that differences in patterns of expression of mRNA may be used to define developmental stage of a cell type (col. 30, lines 10-20 and col. 35, lines 12-29). Fodor fails to provide any hint or suggestion of the claimed invention. Fodor does not teach or suggest methods for determining common response motifs (consensus profiles) in response profiles for a plurality of perturbations, much less in projected profiles or among cellular constituents which co-vary over a plurality of perturbations or which are co-regulated. Nor does Fodor teach or suggest methods for comparing a biological response profile to such a consensus profile; nor does Fodor teach or suggest the other related claims of the instant application, e.g., methods for grouping measured response profiles in sets which are associated with similar biological effects, methods for analyzing response data by grouping co-varying cellular constituents and grouping response profiles with similar effects on cellular constituents, and related methods for determining the therapeutic efficacy of a drug or drug candidate, and for identifying

perturbations that affect cellular constituents. One of ordinary skill in the art would not be motivated to such methods with a reasonable expectation of success from the teachings of Fodor.

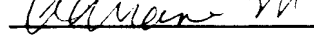
Fodor fails to suggest the claimed invention. Therefore, the presently claimed invention is not made obvious by the cited reference. Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection or objection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the application, are respectfully requested.

Respectfully submitted,

Date June 30, 2000



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